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Infection, inflammation and coagulation disorders - Section 10

Management of coagulation disorders in severe inflammation

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Take home messages

- To understand the main interplay between coagulation system and inflammation and to recognize the key invasive infectious agents causing typical abnormalities in activation of blood platelets, coagulation and fibrinolysis.
- To capture, monitor and follow-up the clinical and laboratory phenotype and the management related to the pathophysiology of inflammation.

Introduction

Inflammation induced by infection results in local tissue damaged followed by systemic endothelial injury, adhesion of platelets and activation of the coagulation cascade. In addition, during infection and inflammation the local control of coagulation fails, triggering the vicious circle of coagulation activating inflammation and vice versa. The hemostatic system represents the first and the most immediate element, programming tissue response to injury and continuum of inflammation, angiogenesis, stromal recruitment and repair.^{*1} Endothelium is under continuous interphase with blood flow. From blood the pathogens and inflammatory mediators invade organ(s), causing vascular damage, microthrombi and multi(organ) failure (eg, sepsis).^{*2} Upon escape of the local regulation of coagulation, typical clinical entities include thrombotic microangiopathy (hemolytic anemia, thrombocytopenia and microthrombi), complement (membrane attack complex) interplay and disseminated intravascular coagulation (DIC).^{*3,4} Inflammation can influence all the three phases of hemostasis and their regulation: (1) megakaryocytes and platelets, (2) coagulation and (3) fibrinolysis (Fig. 1). This short review will provide examples, and some clinical management opportunities in these three phases.

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Current state of the art

The interplay between infection/inflammation and coagulation disorders

During bacterial infection, dual activation of platelets and macrophages can eradicate bacteria in liver.⁵ Strong leukocyte-derived proteolytic enzymes will cleave the anticoagulant and protective endothelial layer of glycosaminoglycans (GAG, ie, heparan sulfate, perlecan and syndecans), exposing von Willebrand factor (VWF), collagen and laminin to trigger platelet deposition, thrombin and fibrin formation (Fig. 1).⁶

Endothelial cells will constitutively secrete VWF, and VWF-size cleaving and controlling ADAMTS-13 enzyme to maintain VWF homeostasis. Infection may consume ADAMTS-13 or lead to antibody formation to exhaust or inactivate its capacity. This can result in the development of thrombotic thrombocytopenic purpura (TTP), or hemolytic uremic syndrome/HUS or atypical, aHUS causing, thrombosis formation in the microvasculature (brain, kidneys) due to platelet- and VWF-rich deposition and complement activation.⁷ Platelets can also bind to endothelial derived-VWF and generated fibrin on the endothelium (thrombocytopenia, “consumption”). Thrombocytopenia, during DIC, may refer to reduced survival in association with severely ill infected patients. The timely therapy of the infection and/or inflammation, including regulation of coagulation may break this vicious loop.^{*8} The main tools to limit excessive coagulation in treating and preventing thrombosis include mainly acetylsalicylic acid, or low-molecular weight heparin (LMWH). If a coagulation defect, that is, low antithrombin is noted and corrected early the balance of coagulation will tilt to a more physiological position.^{*8,9}

The role of megakaryocytes, platelets and thrombin in infection and inflammation

While the hemostatic roles of platelets are well recognized, emerging data demonstrate that megakaryocytes and platelets possess diverse and dynamic functions that also mediate

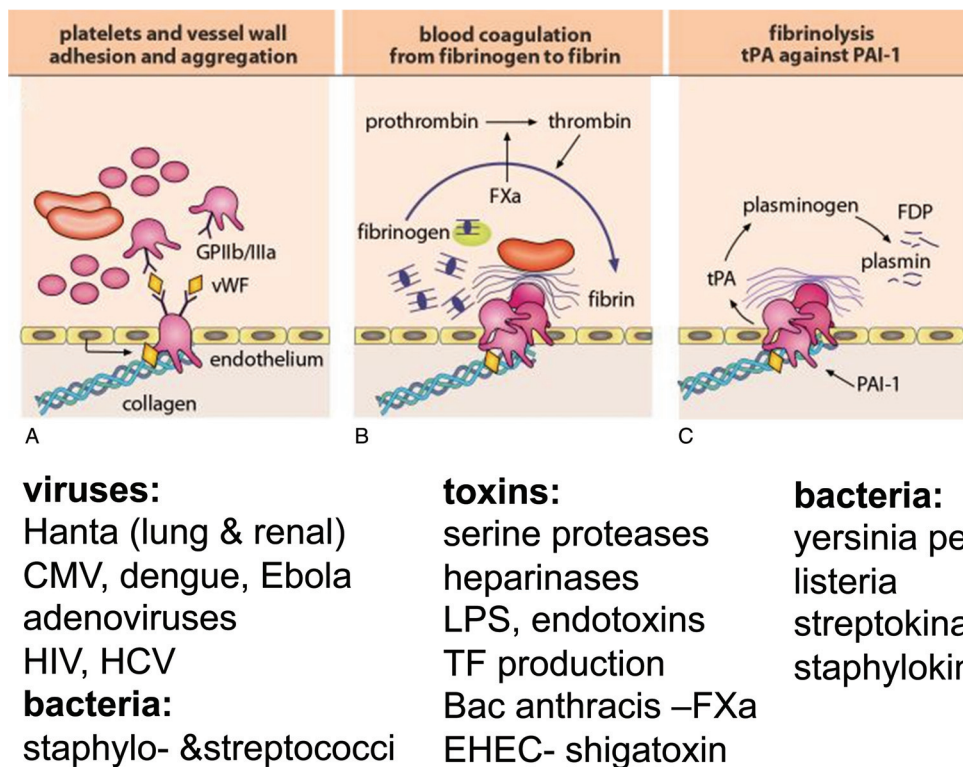


Figure 1. Coagulation targets of some pathogen as examples. Coagulation occurs sequentially: (A) platelet adhesion and activation, (B) thrombin generation and fibrin formation and (C) degradation of fibrin by fibrinolysis. Some infectious agents at each step are presented as examples. CMV = cytomegalovirus, EHEC = Enterohemolytic Escherichia Coli, HCV = hepatitis C virus, HIV = human immunodeficiency virus, LPS = lipopolysaccharide, TF = tissue factor.

inflammatory and immune responses (Table 1).^{10–12} Many infection processes result in thrombocytopenia due to enhanced destruction of megakaryocytes and platelets.^{13–15}

However, megakaryocytes and platelets possess a multitude of innate immune tools, including toll-like receptors, to recognize pathogens, and Fc receptors, which recognize immune complexes.¹⁰ In addition, platelets contain many antimicrobial agents, including antimicrobial peptides and beta-defensins, which directly act on bacterial pathogens.^{10,12,16} Platelets also release chemokines such as platelet factor 4, RANTES and β -thromboglobulin, which increase leukocyte recruitment and survival during viral infections, and can reduce HIV infection by directly interacting with the viral envelope.^{17–19}

Recently, megakaryocytes have been shown to play significant roles in fighting infections. For example, megakaryocytes possess major histocompatibility complex (MHC) I and are capable of endocytosing endogenous antigen.²⁰ Upon processing the antigen through the proteasome, megakaryocytes can present antigens in an MHC-I dependent manner to activate CD8⁺T cells. In addition, viral infections such as influenza and dengue virus significantly

alter the transcriptome of megakaryocyte and platelets, resulting in expression of novel anti-viral molecules such as interferon-induced transmembrane 3 (IFITM3).²¹ Induction of IFITM3 in megakaryocytes and surrounding hemopoietic stem cells reduces viral infection and appear to be mediated through Type I interferon release from the megakaryocyte.

Thrombin activates protease-activated receptors on platelets and endothelial cells and generates fibrin. Thrombin activation of platelets results in release of chemokines and platelet microbicidal proteins to reduce the spread of infection, while fibrin formation allows pathogens to be trapped and cleared by leukocytes.^{16,22,23} Both reduced thrombin generation and enhanced fibrinolysis in mouse models increase susceptibility to bacterial infections, suggesting thrombin, platelets and megakaryocytes play critical roles in stemming the spread of infection, while maintaining hemostasis.²⁴

The effect of pathogen-host interactions on coagulation

Some intriguing observations suggest fibrin formation in addition to its role in ceasing bleeding, recruits macrophages (CD11/18) to limit pathogens from spreading.²⁵ For instance, streptococci and staphylococci will invade the fibrin and surroundings by secreting strepto- and staphylokinase, which will activate matrix metalloproteinases (MMPs) and plasmin to allow the penetration of these pathogens (Fig. 1). Also, severe vascular damage may lead to tissue hemorrhaging, which platelets resist, while hematomas provide a growth media to the bacteria. Listeria sepsis in immunocompromised patients underlines the importance of fibrin (ogen) in limiting the infection from spreading.²⁶ Hantaviruses trigger activation of fibrinolysis in relation to coagulation activity, simultaneously causing temporarily thrombocytopenia.²⁷ Dengue

Table 1

Immune-Related Chemokines/Cytokines Released by Megakaryocytes.

Chemokine/Cytokine	Function
Platelet Factor 4	Monocyte, neutrophil, lymphocyte recruitment
RANTES	Anti-viral protein released from alpha granules
β -thromboglobulin	Neutrophil recruitment and activation
Beta Defensin	Antimicrobial protein released upon activation
Type I Interferon	Cytokines released by megakaryocyte upon viral infection

hemorrhagic fever also induces hyperfibrinolysis and thrombocytopenia through destruction of platelets and megakaryocytes.^{14,15,28}

Influence of Inflammation on coagulation responses

As examples of inflammation, vasculitis and atherosclerosis both impact the coagulation system. Immunological ANCA-vasculitis activates both coagulation and fibrinolysis, which associate with impairment of renal function.²⁹ In individuals with atherosclerosis and impaired distal perfusion of leg arteries, the functional severity of vascular disease relates to the levels of fibrinogen, thrombin-antithrombin complexes and D-dimer.³⁰ Finally, in the management of allogeneic stem cell transplantation the outcome and later graft-versus-host disease are affected by the early and longitudinal maladapted regulation of coagulation.^{31,32} Thus, reduced protein C activity and enhanced thrombin generation, and high FVIII levels, refer to impaired protective effects of endothelium during the transplantation recovery.

Future clinical perspectives

The main approach is to observe the symptoms and signs and rapidly target the causative pathogen and individualize immune- and supportive therapy, including thromboprophylaxis, to eliminate the trigger of inflammation and coagulation disorder (8). A stepwise laboratory follow-up alongside clinical hemostasis abnormalities includes blood cell counts, C-reactive protein assessing the extent of inflammation, antithrombin, fibrinogen, coagulation screening tests of prothrombin time (PT) and activated partial thromboplastin time (APTT), thrombin time, FVIII/VWF, and D-dimer will give a broad overall picture of the potential deficiencies, over-activities (eg, ISTH DIC score), and their tendencies upon active patient management and recovery. Intravenous Vitamin K administration (1-5 mg, 0.15 mg being the daily requirement) corrects PT (FII, FVII, FIX, FX, protein C and S), if the liver synthesis is impaired due to consumption and poor access to vitamin K limited by antibiotics and malabsorption. Short APTT and thrombin time refer to enhanced contact pathway and thrombin activity. The higher the fibrinogen, the poorer the fibrinolytic capacity (D-dimer trends). FVIII/VWF indicates the extent of endothelial damage and low antithrombin may tilt the balance towards uncontrolled thrombin generation. In the future, the global hemostasis assessment, including thrombin generation capacity, will likely aid in the patient management.

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